Scientific Abstract

Cystic fibrosis (CF) is inherited as an autosomal recessive disorder that occurs in approximately 1:2500 live Caucasian births. CF results from mutations in a single gene, the cystic fibrosis transmembrane conductance regulator (CFTR), that encodes a cAMP-regulated chloride channel. This channel is normally expressed on the apical membrane of epithelial cells lining the respiratory and intestinal tracts and sweat glands. It has been suggested that the fluid and electrolyte content of airway mucus is dependent on CFTR activity and that failure to secrete chloride by CF cells results in diminished hydration of mucus, sputum hyperviscosity and the pulmonary sequelae of the disease (1). Diagnosis of CF is based on chronic pulmonary disease and an abnormal sweat chloride concentration of greater than 60 mEq/L. Additional clinical manifestations of the disease occur in the pancreas, liver, intestinal and reproductive tracts, and in the nose and sinus. In spite of the introduction of new treatments and more aggressive management of the disease, more than 90% of CF patients die of lung disease by age 30.

The CFTR gene was cloned in 1989 (2). Although the most common mutation in the CFTR gene is Δ508, a 3 bp deletion that results in deletion of a phenylalanine residue, there are over 400 known mutations that have been identified within the CFTR gene. *In vitro* experiments have shown that introduction of the CFTR gene into cultured CF cells restores normal chloride channel function (3,4). A number of experiments have successfully delivered hCFTR DNA to the airway epithelium of transgenic CF mice and demonstrated correction of the cAMP-regulated chloride efflux (5,6).

CF is an attractive candidate for gene therapy because the disease results from defects in a single gene and because the target organs, the nasal passages and the lungs, are relatively accessible for treatment. Initial attempts in clinical trials using adenoviral delivery of hCFTR to the nasal passages or lungs of CF patients achieved transient expression of CFTR but also elicited dose-dependent inflammatory reactions (7-9). The results of the first study assessing the effect of liposome-mediated delivery of hCFTR to the nasal passages of CF patients were recently reported (10). This study used DC-Chol-DOPE liposomes to deliver hCFTR via nasal spray to nine patients with severe pulmonary disease. There were no adverse events nor was there any evidence of toxicity or inflammation. Five out of eight patients receiving the DNA-lipid complex showed evidence of gene transfer and expression of CFTR. There was a transient correction of approximately 20% of the low chloride perfusion response of the nasal potential difference in these patients. Liposomal delivery may be an attractive alternative to viral delivery as liposomes are relatively nonimmunogenic and non-infectious. In addition, liposomes can be used to deliver large DNA plasmids, do not require cell division to mediate gene transfer, and can be aerosolized.

GR213487B is comprised of the plasmid, pMB113, complexed with cationic liposomes of *p*-ethyl dimyristoyl phosphatidyl choline (EDMPC) and cholesterol. The plasmid, pMB113, contains the hCFTR cDNA under the control of an HCMV enhancer and promoter. The proposed clinical trial will evaluate the safety and biological efficacy of GR213487B in CF patients. The study design will be a double-blind, controlled, dose ranging study in the nasal epithelium of patients with mild to moderate CF. The nasal epithelium has been chosen due to accessibility, similarity to the bronchial epithelium, and the ability for simple, safe, repeat examinations for careful evaluation of the effects of liposomal delivery of hCFTR DNA.

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